REMARKS

Claims 1-14, 29-31, 33-39, 45-49, and 53 are pending in this application. Claims 15-28, 32, 40-44, and 50-52 were previously canceled. Claims 1-3, 11, 29 and 47-49 are amended herein, support for which can be found throughout the specification, for example, at page 20 (listing some examples of the cycloheteroalkyl ring formed by R_1 and R_2 together with the carbon atom to which they are attached). No new matter has been introduced. Upon entry of the present amendments, claims 1-14, 29-31, 33-39, 45-49, and 53 will remain pending.

I. Withdrawal of Prior Rejections

Applicants note with appreciation that the rejections under 35 U.S.C. § 102(b) over Kende et al. (J. Org. Chem. Vol. 55, pp. 1125-26) and the Levin et. al application(WO 00/44723) have not been repeated, and presumably have been withdrawn.

II. Claim Rejections

A. 35 U.S.C. § 102

Claims 1-14, 29-31, 33-39, 45-49, and 53 stand rejected under 35 U.S.C. § 102(a) and 102(e) as allegedly anticipated by WO 00/44723 (the Levin et. al application). The Action alleges that the Levin et. al application teaches a method of making alpha sulfone ester derivatives (i.e., alpha-sulfonyl hydroxamic acid derivatives), citing page 66, Example 24 and page 68, Example 25 specifically.

1. Applicants respectfully submit that the Levin et. al application is not available as prior art under 35 U.S.C. § 102(a), and respectfully request withdrawal of the rejection under 35 U.S.C. § 102(a).

At the outset, Applicants respectfully point out that the present application claims priority to U.S. Provisional No. 60/266,312, filed January 27, 2000. Accordingly the effective filing date of the present application is January 27, 2000. See, e.g., MPEP § 706.02 (stating that "[i]f the application is entitled to priority under 35 U.S.C. 119(e) from a provisional application, the effective filing date is the filing date of the provisional application.") . On the other hand, the publication date of WO 00/44723 (the Levin et. al application) is August 03, 2000. The earliest prior art date under 102(a) for WO 00/44734 is its publication date, which is after the effective

date of the present application. Therefore, the rejection under 35 U.S.C. 102(a) is improper and is respectfully requested to be withdrawn. See MPEP § 706.02(a).II.C (stating that "[f]or 35 U.S.C. 102(a) to apply, the reference must have a publication date earlier in time than the effective filing date of the application").

2. Applicants respectfully submit that the cited reference (the Levin et. al application) is not available as prior art under 35 U.S.C. § 102(e), and respectfully request withdrawal of the rejection under 35 U.S.C. § 102(e).

The international filing date of the Levin et. al application cannot qualify as the prior art date under 35 U.S.C. 102(e).

> If the potential reference resulted from, or claimed the benefit of, an international application, the following must be determined:
> (1) If the international application meets the following three conditions:
> (a) **an international filing date on or after November 29, 2000**;
> (b) designated the United States; and
> (c) published under PCT Article 21(2) in English,
> then the international filing date is a U.S. filing date for prior art purposes under 35 U.S.C. 102(e). (emphasis added)

MPEP § 706.02(f)(1).(C).(1).

Because the filing date of the Levin et. al application is January 27, 2000, the condition that requires the international filing date on or after November 29, 2000 is not satisfied. Indeed, the MPEP provides specific guidance on this question, stating: "[f]or U.S. application publications and **WIPO publications** directly resulting from international applications under PCT Article 21(2), never apply these references under 35 U.S.C. 102(e)" if the international applications have an international filing date prior to November 29, 2000. See MPEP § 706.02(f)(1).(C).(3)(b) (emphasis added). Therefore, Applicants respectfully request that the rejection under 102(e) be withdrawn, and claims 1-14, 29-31, 33-39, 45-49, and 53 be allowed.

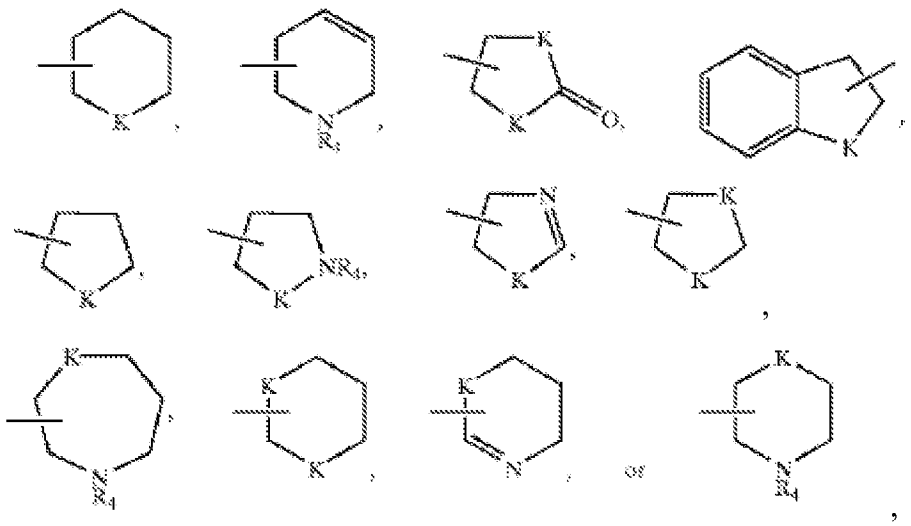
B. 35 U.S.C. § 112

Claims 1-14, 29-31, 33-39, 45-49, and 53 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement and/or the enablement requirement. Applicants respectfully point out that the written description requirement and the enablement requirement are separate requirements. While referring to both requirements, the Office Action provided an explanation of the rejection in terms of lack of

enablement only. Application respectfully submit that the rejection under the written description requirement is improper and the that the claims are in compliance with written description requirement. Moreover, the claims, as currently amended, comply with the enablement requirement.

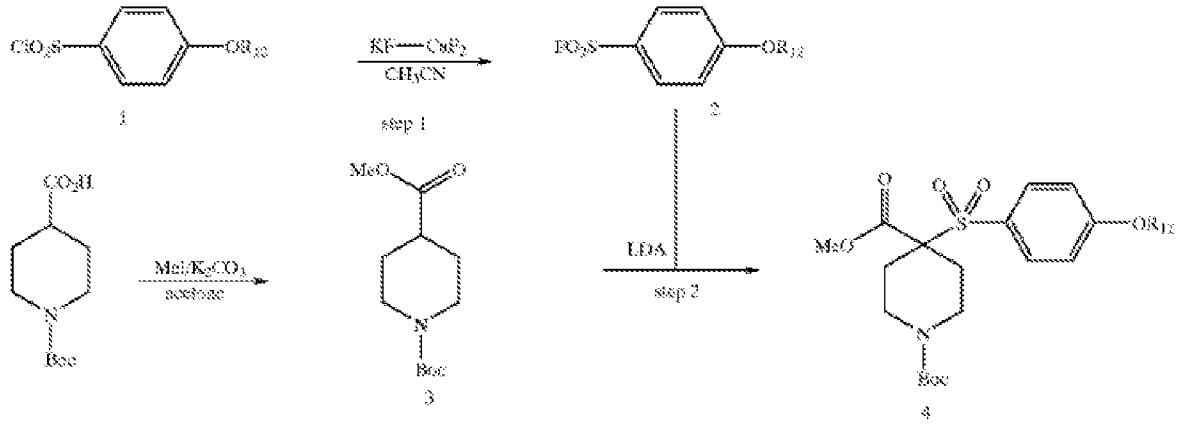
1. More specifically, although conceding that the present application is enabling for compounds of formulas I, V and IX wherein the ring formed by R_1 and R_2 together with the carbon atom to which they are attached is a piperidine ring; Z is CH_3CH_2O-, OH-NH-, OH or CH_3-O-; and R_3 is (substituted) phenyl, the Office asserts that the specification provides no guidance as to what other rings (formed by R_1 and R_2 together with the carbon atom to which they are attached) might be suitable. In addition, the Office asserts that "[t]here is no reasonable basis for assuming that the myriad of compounds embraced by the claim will share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and further would not be produced by the same process." The Office also alleges that "[t]here is insufficient disclosure of starting materials that would place such a diverse genus of compounds in possession of the public in the event of a patent grant." Applicants respectfully disagree with the assertions and reasoning.

Although Applicants believe that the application as filed is fully enabling for the originally filed claims, solely to advance prosecution, claim 1 has been amended to recite that the 5-10 membered cycloheteroalkyl ring formed by R_1 and R_2 together with the carbon atom to which they are attached is



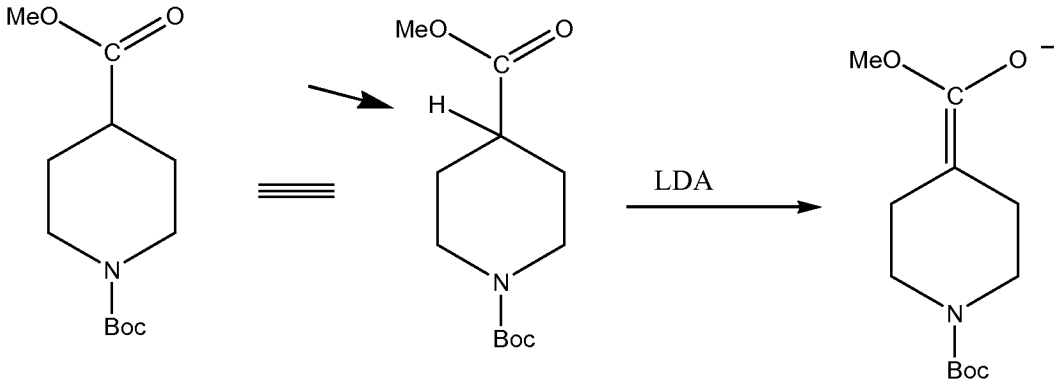
wherein each instance of K is, independently, O, S or NR_4. Support for this amendment can be found, for example, at page 20 of the specification. In view of the present amendment, Applicants respectfully submit that the scope of the pending claims are not unreasonably broad in view of the disclosure of the present application.

Applicants respectfully direct the examiner's attention to pages 24-25 of the specification as originally filed, which provides Scheme I and its corresponding description.



Scheme I, in part

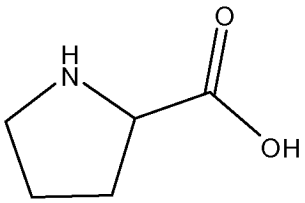
In step 2 of Scheme 1, the enolate (as intermediate, not shown in Scheme I) is prepared from ester 3 (which is in turn prepared by treating commercially available Boc-isonipecotic acid with methyl iodide/potassium and LDA as base):



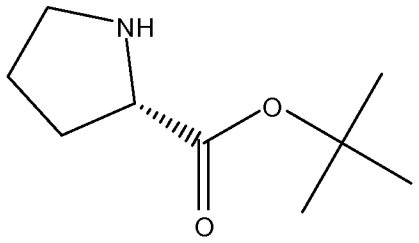
the enolate

One skilled in the art would readily recognize that the enolate is formed because of the proton that is attached to the alpha position of the carbonyl group. Thus, one skilled in the art would recognize from the teaching of the specification to choose other heterocyclic acids and their derivatives (which have one proton attached to the alpha position of the carbonyl group),

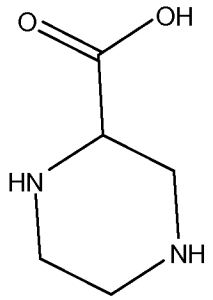
such as those commonly known acids/esters (which can easily be protected by Boc group on the nitrogen):



2-carboxy-pyrrolidine
or proline
CAS #: 609-36-9 ,

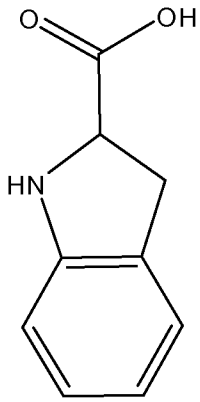


tert-butyl (2S)-2-pyrrolidinecarboxylate
CAS #: 2812-46-6 ,



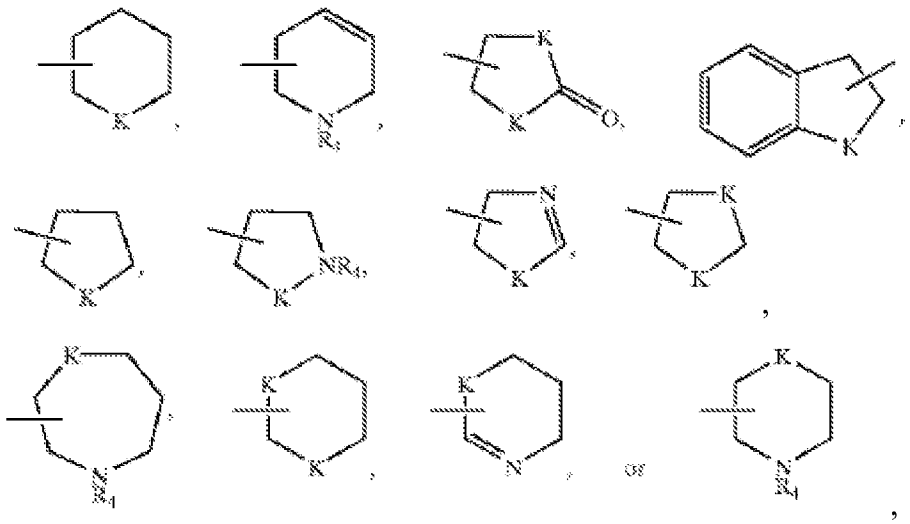
piperazine-2-carboxylic acid

CAS # for the di hydrochloride salt:
3022-15-9



2-indolinecarboxylic acid
or CAS # : 78348-24-9 .

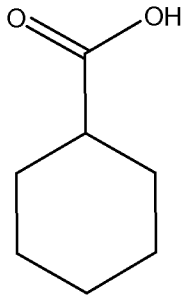
This is true especially when the specification discloses that the 5-10 membered cycloheteroalkyl ring formed by R_1 and R_2 together with the carbon atom to which they are attached can be



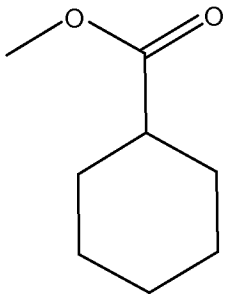
,

wherein each instance of K is, independently, O, S or NR_4. See, page 20 of the specification.

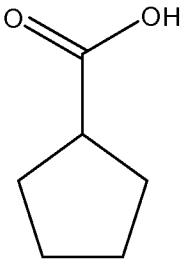
Similarly, one skilled in the art would recognize from the teaching of the specification to choose cycloalkyl acid derivatives, such as those commonly known acids/esters:



cyclohexanecarboxylic acid
CAS #: 98-89-5 ,



methyl cyclohexanecarboxylate
CAS #: 4630-82-4 , or



cyclopentanecarboxylic acid
CAS #: 3400-45-1 .

As the Office correctly points out, the present application is enabling for compounds of formulas V and IX wherein Z is CH_3CH_2O-, OH-NH-, OH or CH_3-O-. Applicants respectfully point out one skilled in the art would be able to convert compounds of formula V wherein Z is H (aldehyde), -NR_5R_6 (amide), OR_5 (ester) to their corresponding acids (which in turn can be converted to alpha-sulfonyl hydroxamic acids) by conventional methods well known in the art. For example, an aldehyde can be oxidized to an acid; an amide an be hydrolyzed to an acid; and an ester can be hydrolyzed to an acid. Moreover, one skilled in the art would readily recognize that an acid compound can be reacted with commercially available hydroxylamine (or its salt) and commercially available (e.g., from Aldrich) substituted hydroxylamines (or their salts) such as O-methylhydroxylamine hydrochloride (CAS #: 593-56-6), O-ethylhydroxylamine hydrochloride (CAS #: 3332-29-4), N,O-dimethylhydroxylamine hydrochloride (CAS #: 6638-79-5), O-allylhydroxylamine hydrochloride (CAS #: 38945-21-0), O-phenylhydroxylamine hydrochloride (CAS #: 6092-80-4), and N-cyclohexylhydroxylamine (CAS #: 2211-64-5). This is so especially because the specification discloses that "hydroxylamine derivative of . . . formula VII [of] XONHY" can be used. See page 10 of the specification. In addition, one skilled in the art would be able to do routine modification (e.g., alkylation) on a -OH or –NH- group using reagents such as alkyl halide or arylalkyl halide (e.g., benzyl bromide) under suitable conditions.

As to R_3, although the examples in the specification only have substituted aryl, one skilled in the art would know other suitable chemical reagents such as alkylsulfonyl halide [such as perfluoro-1-butanesulfonyl fluoride (CAS #: 375-72-4), or methanesulfonyl choloride, which

can be converted to the corresponding fluoride compound], heteroarylsulfonyl halides (such as 5-chlorothiophene-2-sulfonyl chloride, CAS #: 2766-74-7, which can be converted to its corresponding fluoride compound), and heteroaryl thiols (which can be oxidized to heteroarylsulfonyl halides by using NaOCl) such as 4-pyridinethiol, CAS #: 4556-23-4. The specification also directs its readers to look for commercially available sulfonyl halides/chlorides and provides references for the preparation of sulfonyl halides. See page 16 of the specification.

Applicants' exemplary compounds and syntheses are just that: exemplary. Given the schemes and direction provided by Applicants' specification, those skilled in the art would be able to make and use the full range of applicants' claimed invention.

2. The Office Action further rejects the method of treatment claims 48 and 49 under 35 USC § 112, first paragraph, for allegedly lacking enablement.

Applicants has amended claim 48 to recite "[a] method of treating a pathological condition or disorder responsive to inhibition of a TNF-alpha converting enzyme (TACE)." In view of the present amendment, Applicants respectfully submit that claims 48 and 49, as currently amended, satisfy the enablement requirement.

As will be recognized, the enablement requirement of §112 is satisfied so long as a disclosure contains sufficient information that persons skilled in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly

> enabling.... [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Accordingly, the burden is on the PTO to establish that one skilled in the art would doubt the asserted enablement, and the Office must provide reasoning or evidence to shift the burden to the applicant. However, the Office Action provided no such evidence at all and only concluded that the claims are indefinite and not enabled. Therefore, this rejection is improper.

Moreover, it is not sufficient to base a finding of nonenablement on "**merely a disagreement as to the interpretation of the data and the conclusion to be made from the facts**." See *In re Wands,* at 1403-07. (emphasis added)

(A) The breadth of the claims

The claims recite use of compounds of Formula IX (as TACE inhibitors) for treating disorders such as rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection. See e.g., page 1-2 of the specification (explaining the nexus between TACE inhibition and treatment of these disorders and citing references which establish the nexus).

The scope of claims 48-49 is not unduly broad because the application provides sufficient directions to enable those of skill in the art to make and use the full range of applicants' claimed invention. The specification provides ample directions regarding how to make these compounds. Moreover, the specification provides a test procedure for measuring TACE inhibition and data for the exemplary compounds. See e.g., page 75 of the specification.

(B) The nature of the invention

The field of endeavor is the inhibition of TACE enzymes for therapeutic effects. The specification teaches the test procedure and biological data (together with compounds and the method of making thereof).

(C) The state of the prior art

TACE "catalyses the formation of tumor necrosis factor-alpha precursor protein." See page 1 of the specification. "TNF-alpha is a very powerful proinflammatory mediator produced by activated macrophages, blood monocytes, and mast cells." *See* page 2 of the specification.

"In addition to its anti-tumor properties, TNF-alpha is a proinflammatory cytokine that has a central role in rheumatoid arthritis, and Crohn's disease." *See id.* "Animal models and association studies in humans have indicated a potential role for TNF in insulin resistance, multiple sclerosis, organ failure, pulmonary fibrosis, and HIV infection." See id; See also, the last paragraph on page 2 (citing references which establish the nexus between TACE inhibition and treatment of these disorders); and see the references Applicants submitted together with their response filed on December 28, 2006 (establishing the nexus between TACE inhibition and treatment of these disorders).

(D) The level of one of ordinary skill

The level of skill of one working in this field is high.

(E) The level of predictability in the art

TACE "catalyses the formation of tumor necrosis factor-alpha precursor protein." See page 1 of the specification. "TNF-alpha is a very powerful proinflammatory mediator produced by activated macrophages, blood monocytes, and mast cells." *See* page 2 of the specification. "In addition to its anti-tumor properties, TNF-alpha is a proinflammatory cytokine that has a central role in rheumatoid arthritis, and Crohn's disease." *See id.* "Animal models and association studies in humans have indicated a potential role for TNF in insulin resistance, multiple sclerosis, organ failure, pulmonary fibrosis, and HIV infection." See id; See also, the last paragraph on page 2 (citing references which establish the nexus between TACE inhibition and treatment of these disorders); and see the references Applicants submitted together with their response filed on December 28, 2006 (establishing the nexus between TACE inhibition and treatment of these disorders).

The Office Action focuses on the phrase "disease state associate with inhibiting pathological changes mediated by TNF-alpha converting enzymes (TACE)" and alleges the phrase is indefinite. Applicants have amended claim to recite "[a] method of treating a pathological condition or disorder responsive to inhibition of a TNF-alpha converting enzyme (TACE)." In view of the present amendment, Applicants respectfully submit that claims 48 and 49, as currently amended, are clear and definite and satisfy the enablement requirement. Applicant respectfully submit that the disorders in the method of treatment claims are linked to TACE inhibition. See, e.g., pages 1-2. The Office Action does not dispute that the compounds are TACE inhibitors. It is improper to reject the claims because of "merely a disagreement as to

the interpretation of the data and the conclusion to be made from the facts." See *In re Wands,* at 1403-07 and MPEP § 2164.01(a).

(F) The amount of direction provided by the inventor

The application provides detailed schemes (together with descriptions) and many examples (See Examples 14-36 in the specification) to teach how to make the novel compounds. The application further provides detailed test procedures and data regarding TACE inhibition. Again, Applicants emphasize that given the schemes and direction provided by Applicants' specification, those skilled in the art would be able to make the full range of applicants' claimed compounds. See the discussion in Section II.B.1, supra.

(G) The existence of working examples

The application provides Examples 14-26 (pages 38-45 of the specification), teaching how to make the novel compounds and their use as TACE inhibitors (providing biological test and data on page 75 of the specification).

In sum, Applicants respectfully submit that their teachings coupled with the knowledge of those skilled in the art would fully enable one of skill in the art to make and use the full scope of Applicants' claims of treatment of disorders responsive to inhibition of TACE. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 48-49.

3. Claim 48 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

More specifically, the Office asserts that defining a disease by its underlying cause renders the scope of the intended uses indeterminate since the claim language may read on diseases not yet known to be caused by or affected by such action or in ways not yet understood. Applicants respectfully disagree. As would be appreciated by one skilled in the art, the nexus between TACE inhibition and treatment of the disorders (such as rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection) have been established. In view of the disclosure of the application (together with the common knowledge of those skilled in the art) and the current amendment, Applicants

respectfully submit that claim 48, as amended, is clear and definite. Accordingly, Applicants respectfully request withdrawal of this rejection to claim 48.

4. Claims 1-2 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being incomplete for omitting essential steps which amount to a gap between the steps. More specifically, the Office asserts that there is no recitation of how formula V is converted to formula I.

Applicants respectfully disagree. "The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. § 112, second paragraph, is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available." MPEP § 2173.02

> The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with **a reasonable degree of clarity and particularity**. Definiteness of claim language must be analyzed, **not in a vacuum**, but in light of:
>
> (A) **The content of the particular application disclosure;**
>
> (B) The teachings of the prior art; and
>
> (C) **The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made**.

Id. (emphasis added)

The application discloses converting an ester to an acid [see, e.g., page 10 of the specification, hydrolyzing an ester (Z is OR_5, i.e., OEt)], and converting the acid to the final product of hydroxamic acid derivative of formula I using hydroxylamine or hydroxylamine derivative of formula VII: XONHY in the presence of a coupling reagent. See id.; see also pages 14-15 of the specification; and the discussion in Section II.B.1, supra. For another example, an acid of formula V (Z is OH) can be converted to a more reactive species such as acid chloride and then the acid chloride can be converted to the final compound of formula I. See, page 12 of the specification (step d). Thus, one skilled in the art would understand what the claimed conversion means when Z is OH or OR_5. *See also*, the discussion in Section II.B.1, supra.

Moreover, one skilled in the art would be able to convert compounds of formula V wherein Z is H (aldehyde), $-NR_5R_6$ (amide), to their corresponding acids (which in turn can be converted to alpha-sulfonyl hydroxamic acids) by conventional methods well known in the art.

For example, an aldehyde can be oxidized to an acid; an amide an be hydrolyzed to an acid; and an ester can be hydrolyzed to an acid. *See* the discussion in Section II.B.1, supra.

Thus, claims 1-2 set out and circumscribe its step of converting the compound of formula V to the compound of formula I with a reasonable degree of clarity and particularity. One skilled in the art would understand what is required to do the claimed conversion. Accordingly, Applicants respectfully request withdrawal of this rejection to claims 1-2.

In view of the foregoing, Applicants respectfully request reconsideration of the rejections in light of the above comments and amendments. Early allowance of all pending claims is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative at (215) 981-4142 if there are any questions regarding Applicants' claimed invention.

The Commissioner is hereby authorized to debit any fee due or credit any overpayment to deposit account 50-0436.

Respectfully submitted,

/Feng Shao, Reg. # 54733/

Feng Shao, Registration No. **54,733**

Date: September 17, 2007

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